

Attachment 2

FOR INTRAMUSCULAR AND INTRAVENOUS USE

Each vial contains colistimethate sodium or pentasodium colistinmethanesulfonate (150 mg colistin base activity). Colistimethate sodium is a polypeptide antibiotic with an approximate molecular weight of 1750. The empirical formula is $C_{58}H_{105}N_{16}Na_5O_{28}S_5$ and the structural formula is represented below:

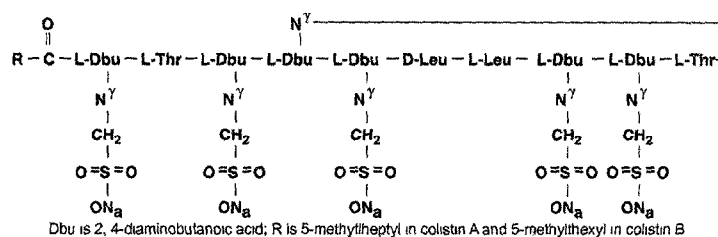


Figure 1

Urine and serum values in adults following Parenteral (IM or IV) administration of Colistimethate for Injection, USP

The graph plots colistin base activity (mcg/mL) on a logarithmic y-axis against time in hours on the x-axis. Two sets of data are shown: Urine (upper lines) and Serum (lower lines). For each, IV is represented by a solid line and IM by a dashed line. Urine activity starts high (around 800-1000 mcg/mL) and decreases over time. Serum activity starts much lower (around 1-20 mcg/mL) and also decreases. The IM route generally shows higher activity than the IV route in both urine and serum at later time points.

Hours	Urine (IV)	Urine (IM)	Serum (IV)	Serum (IM)
1	800	150	20	1.5
2	600	200	8	6
4	300	350	2	7
6	150	200	1	3
8	20	40	0.5	1.5
12	5	10	0.2	0.5

Colistimethate for Injection, USP is indicated for the treatment of acute or chronic infections due to sensitive strains of certain gram-negative bacilli. It is particularly indicated when the infection is caused by sensitive strains of *Pseudomonas*

Colistimethate for Injection, USP

aeruginosa. This antibiotic is not indicated for infections due to *Proteus* or *Neisseria*. Colistimethate for Injection, USP has proven clinically effective in treatment of infections due to the following gram-negative organisms: *Enterobacter aerogenes*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*.

Colistimethate for Injection, USP may be used to initiate therapy in serious infections that are suspected to be due to gram-negative organisms and in the treatment of infections due to susceptible gram-negative pathogenic bacilli.

CONTRAINDICATIONS

The use of Colistimethate for Injection, USP is contraindicated for patients with a history of sensitivity to the drug or any of its components.

WARNINGS

Maximum daily dose should not exceed 5 mg/kg/day (2.3 mg/lb) with normal renal function.

Transient neurological disturbances may occur. These include circumoral paresthesia or numbness, tingling or formication of the extremities, generalized pruritus, vertigo, dizziness, and slurring of speech. For these reasons, patients should be warned not to drive vehicles or use hazardous machinery while on therapy. Reduction of dosage may alleviate symptoms. Therapy need not be discontinued, but such patients should be observed with particular care.

Nephrotoxicity can occur and is probably a dose-dependent effect of colistimethate sodium. These manifestations of nephrotoxicity are reversible following discontinuation of the antibiotic.

Overdosage can result in renal insufficiency, muscle weakness, and apnea (see **OVERDOSAGE** section). See **PRECAUTIONS, Drug Interactions** subsection for use concomitantly with other antibiotics and curariform drugs.

Respiratory arrest has been reported following intramuscular administration of colistimethate sodium. Impaired renal function increases the possibility of apnea and neuromuscular blockade following administration of colistimethate sodium. Therefore, it is important to follow recommended dosing guidelines. See **DOSAGE AND ADMINISTRATION** section for use in renal impairment.

Pseudomembranous colitis has been reported with nearly all antimicrobial agents, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate-to-severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

General

Since Colistimethate for Injection, USP is eliminated mainly by renal excretion, it should be used with caution when the possibility of impaired renal function exists. The decline in renal function with advanced age should be considered.

When actual renal impairment is present, Colistimethate for Injection, USP may be used, but the greatest caution should be exercised and the dosage should be reduced in proportion to the extent of the impairment. Administration of amounts of Colistimethate for Injection, USP in excess of renal excretory capacity will lead to high serum levels and can result in further impairment of renal function, initiating a cycle which, if not recognized, can lead to acute renal insufficiency, renal shutdown, and further concentration of the antibiotic to toxic levels in the body. At this point, interference of nerve transmission at neuromuscular junctions may occur and result in muscle weakness and apnea (see **OVERDOSAGE** section).

Signs indicating the development of impaired renal function include: diminishing urine output, rising BUN and serum creatinine and decreased creatinine clearance. Therapy with Colistimethate for Injection, USP should be discontinued immediately if signs of impaired renal function occur. However, if it is necessary to reinstate the drug, dosing should be adjusted accordingly after drug plasma levels have fallen (see **DOSAGE AND ADMINISTRATION** section).

Drug Interactions

Certain other antibiotics (aminoglycosides and polymyxin) have also been reported to interfere with the nerve transmission at the neuromuscular junction. Based on this reported activity, they should not be given concomitantly with Colistimethate for Injection, USP except with greatest caution.

Curariform muscle relaxants (e.g., tubocurarine) and other drugs, including ether, succinylcholine, gallamine, decamethonium, and sodium citrate, potentiate the neuromuscular blocking effect and should be used with extreme caution in patients being treated with Colistimethate for Injection, USP.

Sodium cephalothin may enhance the nephrotoxicity of Colistimethate for Injection, USP. The concomitant use of sodium cephalothin and Colistimethate for Injection, USP should be avoided.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal carcinogenicity studies and genetic toxicology studies have not been performed with colistimethate sodium. There were no adverse effects on fertility or reproduction in rats at doses of 9.3 mg/kg/day (0.30 times the maximum daily human dose when based on mg/mm²).

Colistimethate for Injection, USP

Pregnancy - Teratogenic Effects

Pregnancy Category C: Colistimethate sodium given intramuscularly during organogenesis to rabbits at 4.15 and 9.3 mg/kg resulted in talipes varus in 2.6% and 2.9% of fetuses, respectively. These doses are 0.25 and 0.55 times the maximum daily human dose based on mg/mm². In addition, increased resorption occurred at 9.3 mg/kg. Colistimethate sodium was not teratogenic in rats at 4.15 or 9.3 mg/kg. These doses are 0.13 and 0.30 times the maximum daily dose based on mg/mm². There are no adequate and well-controlled studies in pregnant women. Since colistimethate sodium is transferred across the placental barrier in humans, it should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether colistimethate sodium is excreted in human breast milk. However, colistin sulphate is excreted in human breast milk. Therefore, caution should be exercised when colistimethate sodium is administered to nursing women.

Geriatric Use

Clinical studies of colistimethate sodium did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Pediatric Use

In clinical studies, colistimethate sodium was administered to the pediatric population (neonates, infants, children and adolescents). Although adverse reactions appear to be similar in the adult and pediatric populations, subjective symptoms of toxicity may not be reported by pediatric patients. Close clinical monitoring of pediatric patients is recommended.

ADVERSE REACTIONS

The following adverse reactions have been reported:

Gastrointestinal: gastrointestinal upset

Nervous System: tingling of extremities and tongue, slurred speech, dizziness, vertigo and paresthesia

Integumentary: generalized itching, urticaria and rash

Body as a Whole: fever

Laboratory Deviations: increased blood urea nitrogen (BUN), elevated creatinine and decreased creatinine clearance

Respiratory System: respiratory distress and apnea

Renal System: nephrotoxicity and decreased urine output

OVERDOSAGE

Overdosage with colistimethate sodium can cause neuromuscular blockade characterized by paresthesia, lethargy, confusion, dizziness, ataxia, nystagmus, disorders of speech and apnea. Respiratory muscle paralysis may lead to apnea, respiratory arrest and death. Overdosage with the drug can also cause acute renal failure, manifested as decreased urine output and increases in serum concentrations of BUN and creatinine.

As in any case of overdose, colistimethate sodium therapy should be discontinued and general supportive measures should be utilized.

It is unknown whether colistimethate sodium can be removed by hemodialysis or peritoneal dialysis in overdose cases.

DOSAGE AND ADMINISTRATION

Important: Colistimethate for Injection, USP is supplied in vials containing colistimethate sodium equivalent to 150 mg colistin base activity per vial.

[Removed reconstitution statement]

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If these conditions are observed, the product should not be used.

Dosage

Adults and pediatric patients—Intravenous or Intramuscular Administration: Colistimethate for Injection, USP should be given in 2 to 4 divided doses at dose levels of 2.5 to 5 mg/kg per day for patients with normal renal function, depending on the severity of the infection.

In obese individuals, dosage should be based on ideal body weight.

The daily dose should be reduced in the presence of renal impairment. Modifications of dosage in the presence of renal impairment are presented in Table 1.

Colistimethate for Injection, USP

Table 1. Suggested Modification of Dosage Schedules of Colistimethate for Injection, USP for Adults with Impaired Renal Function

Renal Function	Degree of Impairment			
	Normal	Mild	Moderate	Considerable
Plasma creatinine, mg/100 mL	0.7 – 1.2	1.3 – 1.5	1.6 – 2.5	2.6 – 4.0
Urea clearance, % of normal	80 – 100	40 – 70	25 – 40	10 – 25
Dosage Unit dose of Colistimethate for Injection USP, mg	100 – 150	75 – 115	66 – 150	100 – 150
Frequency times/day	4 to 2	2	2 or 1	every 36 hr
Total daily dose, mg	300	150 – 230	133 – 150	100
Approximate daily dose, mg/kg/day	5.0	2.5 – 3.8	2.5	1.5

Note: The suggested unit dose is 2.5 – 5 mg/kg; however, the time INTERVAL between injections should be increased in the presence of impaired renal function.

INTRAVENOUS ADMINISTRATION

1. Direct Intermittent Administration - Slowly inject one-half of the total daily dose over a period of 3 to 5 minutes every 12 hours.

2. Continuous Infusion - Slowly inject one-half of the total daily dose over 3 to 5 minutes. Add the remaining half of the total daily dose of Colistimethate for Injection, USP to one of the following:

- 0.9% NaCl
- 5% dextrose in 0.9% NaCl
- 5% dextrose in water
- 5% dextrose in 0.45% NaCl
- 5% dextrose in 0.225% NaCl
- lactated Ringer's solution
- 10% invert sugar solution

There are not sufficient data to recommend usage of Colistimethate for Injection, USP with other drugs or other than the above listed infusion solutions.

Administer the second half of the total daily dose by slow intravenous infusion, starting 1 to 2 hours after the initial dose, over the next 22 to 23 hours. In the presence of impaired renal function, reduce the infusion rate depending on the degree of renal impairment.

The choice of intravenous solution and the volume to be employed are dictated by the requirements of fluid and electrolyte management.

Any infusion solution containing colistimethate sodium should be freshly prepared and used for no longer than 24 hours.

HOW SUPPLIED

Colistimethate for Injection, USP is supplied in vials containing colistimethate sodium (equivalent to 150 mg colistin base per vial) as a clear solution and is available as one vial per carton (NDC XXXXX-XXXX-X).

Store in refrigerator 2° to 8°C (36° to 46°F) and use before expiration date or between 20° to 25°C (68° to 77°F) and use within 7 days.

Rx only.

Manufactured for: